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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/675,509 | 09/29/2000 | Chandler Fulton | 030598.0028.UTL1 | 1879 |

7590 02/04/2003

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|---|---|
| TON, THAIAN N | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 18 |

DATE MAILED: 02/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/675,509 | FULTON ET AL. | |
| | Examiner | Art Unit | |
| | Thai-An N. Ton | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *83* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,10,11 and 16-31* is/are pending in the application.

4a) Of the above claim(s) *16,17 and 20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,10,11, 18, 19, 25-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Applicants' Amendment, filed 11/25/02, Paper No. 17, has been entered. Claims 8, 9, 12, 13, and 14 have been cancelled. Claims 1, 3, 10, 11 and 16-31 are pending.

Newly submitted claims 20-24 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims are directed to methods for identifying a nucleic acid sequence coding for a thaiminase different from *N. gruberi* or *B. thiaminolyticus*.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 20-24 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1, 3, 10, 11, 18, 19, 25-31 are under current examination.

Any rejection made of record in the prior Office action, mailed 5/28/02, Paper No. 16, and not made of record in the instant Office action, has been withdrawn in view of Applicants' arguments and/or amendments to the claims.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 25-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that, "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". This is a written description rejection.

The claimed non-pathogenic bacterium and methods requiring the non-pathogenic bacterium are not described in the instant disclosure, as such, claims 1, 3, 25-31 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP §2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP §2163.02 teaches that, "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to

include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not new matter is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure.*" (emphasis added).

In the instant application, the specification fails to provide adequate written description for non-pathogenic bacterium comprising a recombinant nucleic acid molecule encoding a thiaminase, as required by the claims. Careful review of the specification by the Examiner fails to show where the specification describes a non-pathogenic bacterium, and in further embodiments, bacterium such as Clostridium and Salmonella, which would be constructed and used as claimed in the instant claims. For example, the specification teaches a eukaryotic expression vector which includes a thiaminase, wherein the expression vector is constructed and adapted for expression in eukaryotic cells [see p. 10, lines 7-19]. The specification further teaches that the invention provides a vector which includes a recombinant nucleic acid sequence which encodes a polypeptide thiaminase that is different from *B. thiaminolyticus*, and that the vector is constructed and adapted for expression in prokaryotic cells, such as *E. coli*, although a variety of other bacteria can be used.

[See p. 10, lines 19-27]. However, the specification does not provide description with regard for methods comprising adminstration of a non-pathogenic bacterium comprising a recombinant nucleic acid molecule encoding a thiaminase, as required by the claims. It is further noted that the specification provides no description for non-pathogenic bacteria, as required by the claims. In fact, the claimed "non-pathogenic" bacteria, Clostridium and Salmonella, are well-known in the art to be pathogenic. The Examiner provides references from *Encyclopedia Britannica* which clear show that both bacteria are pathogenic.

Note that the claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing with sufficient, relevant, identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.,* 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiments of non-pathogenic bacterium comprising a recombinant nucleic acid sequence encoding a thiaminase, and methods of using such bacterium for inducing apoptosis in vertebrate cells, lacks written description. The specification fails to describe any non-pathogenic bacterium that would fall into this genus and could be constructed and used as

claimed, and it was unknown, as of Applicants' filing date, that any of these non-pathogenic bacterium would be able to induce apoptosis.

Applicant is reminded that *Vas-Cath Inc. v.* Mahurkar, 19 USPQ2d 1111 [Fed. Cir., 1991] makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The prior rejection of claims 1, 3, 11 and newly added claims 18, 19, 25-31, is *maintained*, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record advanced on pages 3-6 of the prior Office action.

Applicants argue that, with respect to claims 1 and 3, the claims are to methods for inducing apoptosis, and methods for delivering a nucleic acid sequence, thus, the citation of *Fiers v. Revel* and *Amgen v. Chugai* are inapposite, as the claims issued in those cases were not methods claims. Applicants argue that in the instant application, it is described how to deliver thiaminases using conventional delivery methods or using bacterial vectors that encode and express the thiaminase. Further, Applicants argue that they have provided the sequences of two different thiaminases, and identified a variety of organisms from which thiaminases can be

obtained. Applicants argue that as such, no description is lacking for claims 1 and 3.

Applicants' arguments have been considered, however, they are not found persuasive. In particular, MPEP §2163 states that

> An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention.

Although claims 1 and 3 are not directed to products, they are directed to methods, which require a particular product, "cells comprising a thiaminase or derivative thereof, or a non-pathogenic bacterium comprising a recombinant nucleic acid molecule encoding said thiaminase or derivative." It is reiterated that although the specification provides adequate written description for a nucleic acid sequence encoding thiaminase I from *N. gruberi*, the specification fails to describe nucleic acid sequences encoding thiaminases or derivatives thereof. As such, the claimed invention does not meet the written description requirement in that the specification does not provide a description of the claimed invention with all its

limitations, as stated in MPEP §2163, for example, figures, diagrams, formulas or structures, etc. Although the specification contemplates that the thiaminases from other organisms would be "anticipated" to be clear homologues, the specification does not provide sufficient description with particularity to indicate that Applicants had possession of the claimed invention. In particular, the specification fails to meet the written description requirement with regard to the claimed embodiment of nucleic acid sequences encoding thiaminases or derivatives thereof isolated from species other than *N. gruberi*, or nucleic acid sequences encoding derivatives of thiaminase I isolated from from *Naegleria gruberi* lacks written description.

Applicants further argue that newly added claims 18 and 19 are directed to nucleic acid sequences and claims 25-27 are directed to bacteria that encode a thiaminase. Applicants submit that the present rejection is inapplicable to the present claims, directed to nucleic acids, and further, description of a bacteria encoding a recombinant thiaminase is sufficiently described by the indication of suitable bacteria. See pp. 5-6, bridging ¶ of the specification.

Applicants' arguments have been carefully considered, however, they are not found to be persuasive. With regard to newly added claims 25-27, the claimed "thiaminase" is lacks written description. In particular, the term encompasses a broad range of thiaminases, however, the specification has only provided adequate written description of a nucleic acid encoding thiaminase I from *N. gruberi*. The specification fails to adequately describe the broad genus encompassed by the term

"thiaminase". It is reiterated that the skilled artisan cannot envision all thiaminases genes isolated from species other than *N. gruberi*, or nucleic acid sequences encoding derivatives of thiaminase I isolated from *Naegleria gruberi*; therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it.

Therefore, as no nucleic acid sequences encoding thiaminases or derivatives thereof isolated from other species, or nucleic acid sequences encoding derivatives of thiaminase I isolated from *Naegleria gruberi*, they do not meet the written description provision of 35 U.S.C. § 112.

Additionally, the claims as amended are directed to non-pathogenic bacterium which comprise a recombinant nucleic acid for uses in inducing apoptosis and *in vivo* delivery of a thiaminase [see claims 1,3 and their dependent claims]. However, the specification does not provide adequate written description for such bacterium. In particular, the specification teaches that various expression vectors can be constructed and used for expression in human cells, such as non-viral vectors, or vectors that are adapted for expression in prokaryotic or eukaryotic cells. However, the specification provides no guidance or teachings with particularity to show adequate written description with regard to non-pathogenic bacterium which comprise a recombinant nucleic acid encoding thiaminase or a derivative thereof,

used in methods of inducing apoptosis in vertebrate cells or methods for delivering a thiaminase or derivative thereof to vertebrate cells *in vivo*. Accordingly, as the specification does not disclose such bacterium or uses of said non-pathogenic bacterium, they do not meet the written description provision of 35 U.S.C. §112.

The prior rejection of claims 1, 3, 11 and newly added claims 26-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid sequence encoding thiaminase I from *Naegleria gruberi*, vectors containing a nucleic acid sequence encoding thiaminase I from *Naegleria gruberi* operatively linked to a promoter, and cells transformed *in vitro* by said vector, and non-pathogenic bacterium comprising a nucleic acid sequence encoding thiaminase I from *Naegleria gruberi,* the specification does not reasonably provide enablement for methods of inducing apoptosis in a selected group of vertebrate cells *in vivo*, comprising administering to a vertebrate a thiaminase or derivative thereof or a non-pathogenic bacterium comprising a nucleic acid molecule encoding said thiaminase or derivative targeted to said selected group of vertebrate cells, thereby reducing the level of thiamin in said cells sufficiently to induce apoptosis of said cells, methods for delivering a nucleic acid sequence encoding a thiaminase or derivative to vertebrate cells *in vivo*, eukaryotic cells that have been transformed with a eukaryotic expression vector comprising a nucleic acid sequence encoding a thiaminase derivative *in vivo*, or non-pathogenic bacterium encoding a

recombinant nucleic acid sequence encoding a thiaminase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants state that the Examiner asserted that the claimed invention encompasses gene therapy and that Applicant traverses the rejection as they may be considered in connection with the present claims. Applicants argue that the present claims do not concern transfection of human cells, and thus, the references cited by the Examiner in the prior Office action are inapplicable to the present claims. See p. 6, ¶ 2-3 of the Response.

Applicants' argument is not found persuasive. It is noted that the claims as amended continue to read on gene therapy. For example, claim 1 recites a method of inducing apoptosis of a selected group of vertebrate cells *in vivo*, comprising administering to a vertebrate comprising said cells a thiaminase or derivative thereof or a non-pathogenic bacterium comprising a recombinant nucleic acid encoding said thiaminase or derivative targeted to a selected group of vertebrate cells, thereby reducing the level of thiamin in said cells sufficiently to induce apoptosis in said cells. As such, claim 1 encompasses the transfection of human cells. Furthermore, Applicants' have failed to provide teachings or guidance to overcome the unpredictabilities associated with the art of gene therapy. For example, adminstration of a thiaminase or derivative thereof to a cell encompasses

administration of a nucleic acid encoding thiaminase. Furthermore, it is noted that the target cells are vertebrate cells, and humans are vertebrates.

Thus, it is maintained that unpredictable factors cited in the prior Office action, such as levels and duration of gene expression, as well as the poor targeting, and the amount and stability of the protein produced have not been overcome by the instant specification or Applicants' arguments. For example, the amended claims now read on utilizing a non-pathogenic bacterium comprising a recombinant nucleic acid molecule to deliver a thiaminase or derivative thereof to vertebrate cells. As such, the thiaminase would have to be expressed for levels and duration sufficient to reduce the levels of thiamin and induce apoptosis.

Furthermore, with regard to the recitation of "non-pathogenic bacterium", it is noted that the specification provides no teachings or guidance as to what non-pathogenic bacterium could be constructed and used as required by the claims. It is noted that in further embodiments, the claims recite that the non-pathogenic bacterium are Clostridium and Salmonella [see claims 26 and 27]; however, both species of bacterium are well-known in the art to be pathogenic. The Examiner provides references from *Encyclopedia Britannica* which clear show that both bacteria are pathogenic.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters listed above for achieving thiaminase gene therapy, the lack of guidance or direction provided by the specification to carry out thiaminase

gene therapy as broadly claimed, the lack of working examples provided by the specification for the demonstration or correlation to inducing apoptosis or achieving therapeutic thiaminase gene expression *in vivo*, the unpredictable and undeveloped state of the art with respect to the gene therapy art, it would have required undue experimentation for one of skill in the art to make and/or use the claimed vectors, bacterium, and methods of using the same.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Applicants argue that with respect to claim 1, the presence of thiaminase around a cell reduces the level of thiamin, which can then induce apoptosis. Further, Applicants argue that the term thiaminase "derivatives" were described in the '596 and related PCT application, which were incorporated by reference. See p. 6 of the Response. Applicants' arguments have been considered and they are found to be persuasive in view of p. 6, lines 5-9, of the specification, which states that the thiaminase derivatives maintain a thiamin-cleaving and/or thiamin-binding activity.

Claim 25, as written, is unclear. The claim states that the non-pathogenic bacterium encodes a recombinant nucleic acid sequence encoding a thiaminase. It

is unclear how a bacterium can encode a nucleic acid. Claims 26 and 27 depend from claim 25.

*Conclusion*

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

TNT

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